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TITLE: Preventing Epilepsy after Traumatic Brain Injury

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14. ABSTRACT:

The purpose of this study is to determine the safety and tolerability of topiramate in the treatment of early seizures following traumatic brain injury (TBI), and to compare the efficacy of topiramate to prevent of early seizures to the standard of care (phenytoin). A secondary objective is to obtain data necessary to design of a randomized clinical trial to determine if topiramate can prevent epilepsy and improve neurological outcome after TBI. In the first year of the study, we formulated the protocol, informed consent, and other documents required by regulatory bodies. All of these were submitted to the IRB at the University of Pennsylvania, HSRRB at the USArmy, and the FDA. The approval process for this protocol, especially from the HSRRB, including revisions, took approximately one year. During this time we established the infrastructure for the study, hired relevant personnel and organized the patient recruitment methods, interactions with the trauma center, neurosurgical services, EEG laboratory, pharmacy, etc. in order to conduct the research. Patient recruitment is now commencing.

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INTRODUCTION:

The purpose of this study is to determine the safety and tolerability of topiramate (Topamax®) in the treatment of early seizures following traumatic brain injury (TBI), and to determine if topiramate can prevent early seizures better than the current standard of care (phenytoin). A secondary objective is to obtain data necessary to design of a randomized clinical trial to determine if topiramate can prevent epilepsy and improve neurological outcome after TBI. Approximately 90 patients at the University of Pennsylvania will participate in this study. Patients with moderate to severe head trauma who meet entry criteria will be randomized to one of three arms of the study. One arm will receive topiramate for seven days, the second arm will receive topiramate for three months, and the third, control, arm will receive phenytoin for seven days (current standard of care). EEGs will be performed continuously for seven days from onset of the study (within 24 hours of TBI). The patients will be monitored for clinical seizures, subclinical, electrographic seizures, and recovery of function. Additional EEG analyses will examine potential biomarkers for epileptogenesis. Patients will also have MRI scans at one month and twelve months to assess structural damage to the brain. Patients will be followed for two years to determine if epilepsy subsequently develops and to assess level of functional recovery.

BODY:

The original Statement of Work indicated two sets of projects to be accomplished in the first year of the grant. We have substantially completed most of these objectives.

In the first year of the study, we formulated the protocol for the clinical trial, created case report forms and case books, developed the informed consent documents and other documents required by regulatory bodies. All of these were submitted to the IRB at the University of Pennsylvania, the US Army HSRRB, and the FDA. The approval process for this protocol, especially from the HSRRB, took approximately one year. During this time we established the infrastructure for the study, hired relevant personnel and organized the patient recruitment methods, interactions with the trauma center, neurosurgical services, EEG laboratory, pharmacy, etc. in order to conduct the research. Patient recruitment is now commencing.

Below we present the original SOWs (in italics) and our accomplishments:

SOW - Task 1: *Develop instruments for a pilot (and subsequently, full) clinical trial for epilepsy prevention after head injury.* This has been accomplished by the development of the clinical trial protocol, informed consent, case books, and regulatory documents. All of these have received approvals by the University of Pennsylvania IRB, the USArmy HSRRB, and the FDA. This approval process took approximately one year to complete. The most prolonged component was the HSRRB.

a. *Develop the web-based clinical trial instrument now being tested at the University of Pennsylvania for use in clinical trial for epilepsy prevention after head injury. (This study management tool will act as the primary system for managing all aspects of the clinical trial, including functioning as a central repository of all research studies and associated personnel, budget set-up and financial tracking, self-population of standard forms, tracking of IRB and other regulatory approvals, subject scheduling and processing, and overall study tracking. It is expected that once this instrument is fully implemented for this neuroprotection study, it will be easily reformulated for other neuroprotection trials.)* We have accomplished this task but have not yet incorporated the web based clinical trial instrument. Instead, we developed these tools internally. We expect to attempt to employ a web based mechanism as the trial progress.

b. *Develop web-based clinical data base for use in epilepsy prevention trial.* Similarly, we chose to use a simpler, more easily available data base for the early pilot program, as the expense for developing a more comprehensive web-based data base was beyond our budgetary capacity.
c. *Develop brain image data base (BRAID) that can be combined with the clinical data base for use in epilepsy prevention trial.* We are collaborating with the neuroradiology group at the University of Pennsylvania to collect MRI data on the TBI patients in the study and incorporate these images into a BRAID data base being developed at the University.
d. *Combine instruments developed in above into a specific clinical protocol for a 3 arm study designed to prevent epilepsy after moderate to severe head injury.* This has been accomplished and has passed all regulatory requirements.

SOW - Task 2: *Develop the infrastructure for implementation of randomized double blind trial to prevent epilepsy after head injury.* This has been accomplished.

a. Establish procedures with trauma team and ER personnel for identifying candidates for epilepsy prevention trial. We have mobilized collaborators in the ER and in the Trauma Unit to participate in the study. We have held a number of meetings with the teams to provide in service training and will continue to do so as the protocol launches. Most specifically, we are utilizing a unique resource here at the University of Pennsylvania to identify potential subjects and notify study personnel. Our ER has established a program whereby talented and highly motivated premedical students work in our ER every day and night to identify candidates for various clinical trials that originate in the ER. They are being trained to identify suitable candidates for our TBI study and will notify us as soon as such patients reach the trauma bay in the ER.
b. Establish procedures to obtain appropriate consent from patients that are too impaired to provide conventional informed consent. This would involve obtaining consent from individuals who are legally identified as being able to provide consent or by obtaining community consent. This has been accomplished to the satisfaction of all regulatory bodies involved. This is not a trivial issue, since most of the patients will arrive to the ER in a state that will prevent them from being able to provide informed consent (e.g. either comatose or mentally impaired). Our protocol currently requires administration of the first dose of antiseizure drug by 12 hours from the TBI, so we need to reach the appropriate, legally sanctioned individual associated with each patient to provide informed consent. This could not be done with "community consent" under current HSRRB guidelines, and we were not permitted to obtain informed consent over the telephone, even temporarily. Thus, we must rely on being able to communicate directly with appropriate surrogates within 12 hours of the TBI. This requires that our study personnel, mainly physicians and EEG technologist, be available 7 days per week, 24 hours per day.
c. *Develop and promulgate standardized treatment protocol for head injured patients* This was accomplished in collaboration with our neurosurgical team.
d. *Establish pharmacy program for administration of study medications in a double blind manner.* This was accomplished with the HUP pharmacy.
e. Establish procedures for obtaining continuous EEG monitoring for 7 days post head injury. This was accomplished by recruiting a talented EEG technologist to perform and monitor these tests and be dedicated to this protocol. She already has experience performing continuous EEGs on TBI patients for a preliminary study (without drug intervention) that we have begun at the University of Pennsylvania.
f. *Establish internal and external data and patient safety monitoring boards.* We have an internal safety review process and are in the process of establishing an external DSMB. This is not required by the regulatory bodies, but we thought it would be a useful addition to the study.

KEY RESEARCH ACCOMPLISHMENTS:

- Write clinical protocol
- Develop informed consents
- Develop case report forms
- Develop data base
- Submit documents to University of Pennsylvania IRB and obtain approval
- Submit documents to US Army HSRRB and obtain approval
- Submit documents to FDA and obtain IND
- Recruit EEG technologist
- Arrange for randomized drug distribution with Pharmacy
- Arrange collaborative efforts with emergency room, neurosurgery and trauma units
- Establish mechanism for rapid identification of subjects upon arrival in trauma unit
- Develop in service training for relevant personnel
- Establish brain imaging protocols

REPORTABLE OUTCOMES:

To date, there are no reportable outcomes, as the clinical trial protocol is just getting launched.

CONCLUSION:

In the first year of this grant we have successfully completed all the pretrial components and are about to begin entering patients. This includes having performed EEGs on TBI patients who are not part of this research protocol and who did not receive any specific anti-epileptogenic seizure intervention beyond current standard of care. Developing the infrastructure for this kind of trial and successfully navigating all the potential issues in an acute intervention trial in very injured patients was not a trivial task. Similarly, coordinating multiple medical teams, each of which is focused on their own tasks with regard to major trauma cases (e.g. trauma surgeons, neurosurgeons, emergency room personnel, nurses, pharmacy, etc.) was also a significant accomplishment.

One major disappointment at present relates to establishing a more general, comprehensive data base that would be used in this study and would then be available for other studies of anti-epileptogenesis and neuroprotection. To do this on a large scale and to incorporate all the elements needed that would allow the data entered into such a data base to meet FDA standards for drug or treatment registration was much more expensive than we had estimated in our initial proposal. We new that we had underestimated this expense but it was necessary to keep our budget under the DOD cap. That level of funding would just about allow the accomplishment of the pilot trial. Thus, we are utilizing a simpler data base for our current activities with the hope that it will be transposed into the more sophisticated data base when our pilot trial is completed and/or when additional funding becomes available.

By contrast to our mild disappointment about the data base development, we have a achieved a more significant accomplishment with regard to a very important issue related to this study and one which was not submitted as a major part of this grant. We have initiated a program in conjunction with the

National Institutes of Neurological Diseases and Stroke to hold a conference on biomarkers of epileptogenesis. Our reasoning was that we were developing a unique resource for trying to study this issue in humans as an adjunct to our study and with no additional risk to our patients. We are collaborating with the only two groups in the US who have been, or are currently, engaged in epilepsy prevention trials – The University of Washington (who just completed their third, unfortunately negative, clinical trial to prevent epilepsy after TBI) and a group in Washington, DC launching a small pilot trial of preventing epilepsy after TBI (although with less severely injured patients than we are studying and without continuous EEG recordings). This conference will bring together researchers at both the clinical level and animal model level to consider what is known about the process of epileptogenesis and how we might develop biomarkers of the process using electrophysiology (including highly sophisticated signal processing techniques that are not standard in this field), imaging, biochemical markers in CSF and serum, and genomics.

REFERENCES: N/A

APPENDICES: N/A

SUPPORTING DATA: N/A